Remarks

By way of this Preliminary Amendment, claims 1-8, 10, 11 and 13-21 are pending. Claims 9 and 12 have been canceled. Claims 4, 6, 7, 8 and 13-18 have been amended to put the claims in a format appropriate for U.S. prosecution. Claims 19-21 have been added to include material deleted from amended claims 6 and 18. No new matter has been added by way of these amendments.

More specifically, claim 4 has been amended to specify that it is dependent on claim 1. Claim 6 has been amended to specify that R^1, R^2, R^3, R^{36}, R^{37}, R^{38}, R^{39}, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, X, Y and A are as defined in Claim 1. Additionally, claim 6 has been amended to remove phrases such as "if appropriate," "preferably," and "customary". Material deleted from Claim 6 has been rewritten in new claims 19 and 20. Claim 8 has been amended to add the recitation of a pharmaceutically acceptable carrier to the claim. Claims 13-18 have been amended to convert the Swiss-type use claim to the U.S. method of treatment format. Finally, claim 18 has been amended so that the claim contains the proper multiple dependent claim format in compliance with 37 C.F.R. § 1.75(c) and to separate the claim into two independent claims. Material deleted from claim 18 has been rewritten in independent form in new claim 21.

Conclusion

Applicants respectfully submit that the pending claims, as amended, are in condition for allowance. Please charge any fees due with this amendment to deposit account number 13-3372. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: March 22, 2001

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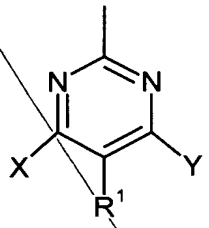
4. (Amended) Compounds according to claim 1,

in which

R^1, X and Y are attached to the pyrimidine ring as follows



and

R^1 represents an optionally substituted cyclopropyl, cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexyl, 1-hydroxycyclopropyl or 1-(fluoromethyl)cyclopropyl radical,

X represents NH_2

and

Y represents hydrogen or NH_2.

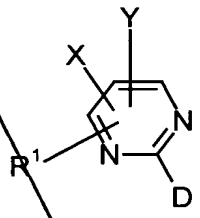
6. (Amended) Process for preparing the compounds of the general formula (I) according to Claim 1,
characterized in that,

depending on the various meanings of the heterocycles listed above under R^2 and R^3,

B1 cont

A2 cont

[A] compounds of the general formula (II)



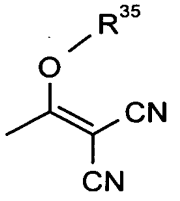
(II),

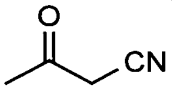
in which

R^1, X and Y are each as defined above in claim 1,

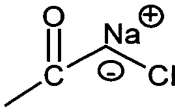
and

D represents radicals of the formulae





or



in which

R^{38} represents C_1-C_4-alkyl

are converted, by reaction with compounds of the general formula (III)

$$A\text{-}CH_2\text{-}NH\text{-}NH_2 \qquad (III),$$

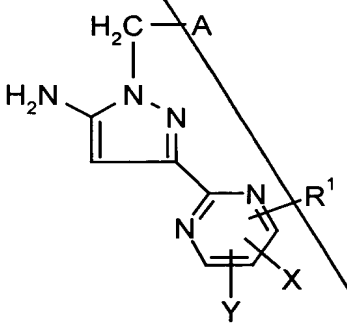
in which

B' cont

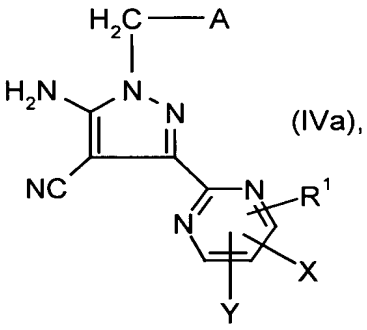
A2 cont

A is as defined above in claim 1,

in inert solvents into the compounds of the general formula (IV) or (IVa)



(IV) and



(IVa),

in which

A, X, Y and R^1 are each as defined above in claim 1,

and, in the case of the compounds of the general formula (IVa), are subsequently cyclized with carboxylic acids, nitriles, formamides or guanidium salts,

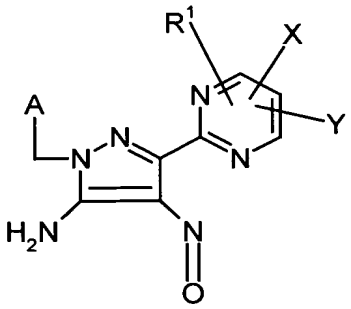
and, in the case of the compounds of the general formula (IV), are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids,

or

[B] in the case that R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are initially converted by nitrosation into the compounds of the general formula (V)

B1 cont

A2 Cont

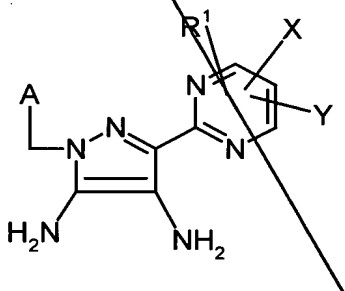


(V),

in which

A, X, Y and R^1 are each as defined above in claim 1,

in a second step, the compounds of the general formula (VI)



(VI),

in which

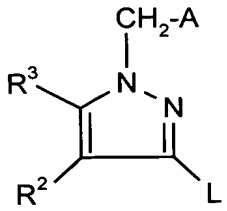
A, X, Y and R^1 are each as defined above in claim 1,

are prepared by a reduction,

and these are subsequently cyclized with 1,2-dicarbonyl compounds,

or

[C] compounds of the general formula (VII)



(VII),

in which

A^1, R^2 and R^3 are each as defined above in claim 1,

and

L represents a radical of the formula $-SnR^{36}R^{37}R^{38}$, ZnR^{39}, iodine, bromine or triflate,

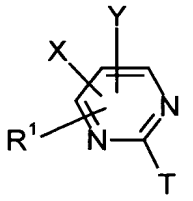
in which

R^{36}, R^{37} and R^{38} are identical or different and each represents straight-chain or branched alkyl having up to 4 carbon atoms

and

R^{39} represents halogen

are reacted with compounds of the general formula (VIII)



(VIII),

in which

X, Y and R^1 are each as defined above in claim 1,

and

in the case that L = $SnR^{36}R^{37}R^{38}$ or ZnR^{39},

T represents triflate or represents halogen,

and,

in the case that L = iodine, bromine or triflate,

T represents a radical of the formula $SnR^{36'}R^{37'}R^{38'}$, $ZnR^{39'}$ or $BR^{40'}R^{41'}$,

in which

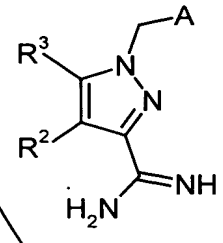
$R^{36'}$, $R^{37'}$, $R^{38'}$ and $R^{39'}$ have the meanings of R^{36}, R^{37}, R^{38} and R^{39} given above in claim 1 and are identical to or different from them,

R^{40} and R^{41} are identical or different and each represent hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring

in a palladium-catalysed reaction in inert solvents,

or

[D] amidines of the general formula (IX)

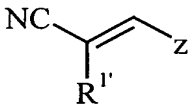


(IX),

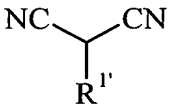
in which

A, R^2 and R^3 are each as defined above in claim 1,

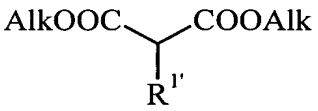
are reacted with compounds of the general formula (X), (Xa), (Xb) or (Xc)



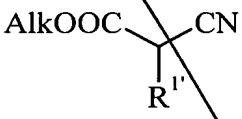
(X)



(Xa)



(Xb)



(Xc),

in which

$R^{1'}$ represents the optionally substituted cycloalkyl radical listed above under R^1;

Alk represents straight-chain or branched alkyl having up to 8 carbon atoms,

and

B1 cont A3 cont

Z represents an NH_2 group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbon atoms, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aroyloxy having 6 to 10 carbon atoms,

and the substituents listed under X, Y, R^1, R^2, R^3 and/or A are modified or introduced by acylation and derivatization of free amino groups, chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

C2 cont

8. (Amended) Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 and a pharmaceutically acceptable carrier.

C2 C A3

13. (Amended) A method of treating a cardiovascular disease, comprising administering to a mammal an effective amount of a compound according to Claim 1.

14. (Amended) The method of claim 13, wherein said cardiovascular disease is hypertension.

15. (Amended) A method of treating thromboembolic disorders and ischaemia, comprising administering to a mammal an effective amount of a compound according to claim 1.

16. (Amended) A method of treating sexual dysfunction, comprising administering to a mammal an effective amount of a compound according to claim 1.

17. (Amended) A method of treating inflammation, comprising administering to a mammal an effective amount of a compound according to claim 1.

A3 Cont C2 cont

18. (Amended) The method of claim 13, 14, 15, 16 or 17, wherein said compound of the general formula (I) according to Claim 1 is administered in combination with an organic nitrate or NO donor.

C² cont

A4

19. (New) The process of claim 6, wherein said compound of the general formula (IV) further are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines in the presence of acids under microwave irradiation.

20. (New) The process of claim 6, wherein said 1,2-dicarbonyl compound is aqueous glyoxal solution.

C² cont

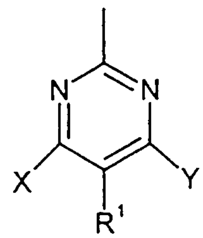
21. (New) The method of claim 13, 14, 15, 16 or 17, wherein said compound of the general formula (I) according to Claim 1 is administered in combination with a compound that inhibits the degradation of cyclic guanosine monophosphate (cGMP).

Version with Markings to Show Changes Made

4. Compounds according to Claim 1 ~~any of the preceding claims,~~

in which

R^1, X and Y are attached to the pyrimidine ring as follows



and

R^1 represents an optionally substituted cyclopropyl, cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexyl, 1-hydroxycyclopropyl or 1-(fluoromethyl)cyclopropyl radical,

X represents NH_2

and

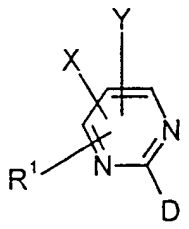
Y represents hydrogen or NH_2.

5. Compounds according to claim 4, in which R^1 represents an optionally substituted cyclopropyl radical.

6. Process for preparing the compounds of the general formula (I) according to Claim 1,
characterized in that,

depending on the various meanings of the heterocycles listed above under R^2 and R^3,

[A] compounds of the general formula (II)



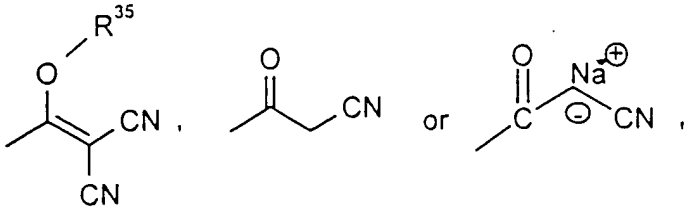
(II),

in which

R^1, X and Y are each as defined above in Claim 1,

and

D represents radicals of the formulae



in which

R^{38} represents C_1-C_4-alkyl

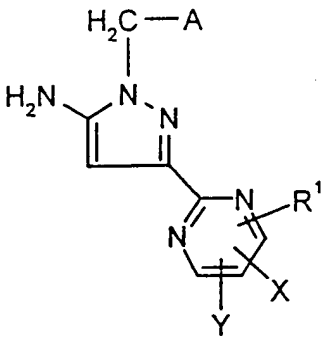
are converted, by reaction with compounds of the general formula (III)

$$A\text{-}CH_2\text{-}NH\text{-}NH_2 \qquad (III),$$

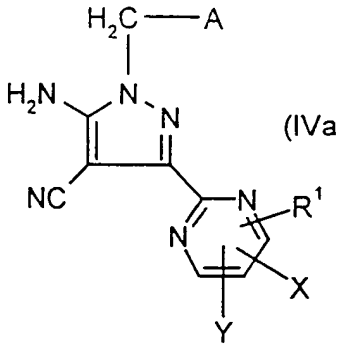
in which

A is as defined above in Claim 1,

in inert solvents, ~~if appropriate in the presence of a base,~~ into the compounds of the general formula (IV) or (IVa)



(IV) and



(IVa),

in which

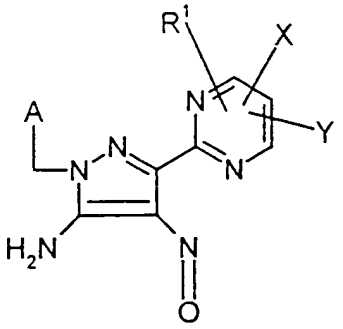
A, X, Y and R^1 are each as defined above, in Claim 1

and, in the case of the compounds of the general formula (IVa), are subsequently cyclized with carboxylic acids, nitriles, formamides or guanidium salts,

and, in the case of the compounds of the general formula (IV), are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids ~~and, if appropriate, under microwave irradiation,~~

or

[B] in the case that R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are initially converted by nitrosation into the compounds of the general formula (V)

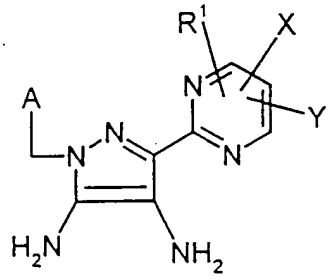


(V),

in which

A, X, Y and R^1 are each as defined above in Claim 1

in a second step, the compounds of the general formula (VI)



(VI),

in which

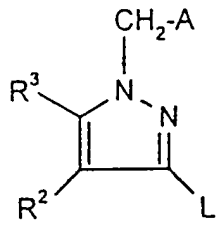
A, X, Y and R^1 are each as defined above in Claim 1,

are prepared by a reduction,

and these are subsequently cyclized with 1,2-dicarbonyl compounds, ~~preferably aqueous glyoxal solution~~,

or

[C] compounds of the general formula (VII)



(VII),

in which

A^1, R^2 and R^3 are each as defined above in Claim 1,

and

L represents a radical of the formula $-SnR^{36}R^{37}R^{38}$, ZnR^{39}, iodine, bromine or triflate,

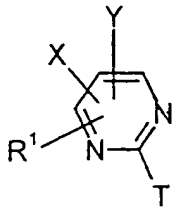
in which

R^{36}, R^{37} and R^{38} are identical or different and each represents straight-chain or branched alkyl having up to 4 carbon atoms

and

R^{39} represents halogen

are reacted with compounds of the general formula (VIII)



(VIII),

in which

X, Y and R^1 are each as defined above in Claim 1,

and

in the case that L = $SnR^{36}R^{37}R^{38}$ or ZnR^{39},

T represents triflate or represents halogen, ~~preferably bromine~~

and,

in the case that L = iodine, bromine or triflate,

T represents a radical of the formula $SnR^{36'}R^{37'}R^{38'}$, $ZnR^{39'}$ or $BR^{40'}R^{41'}$,

in which

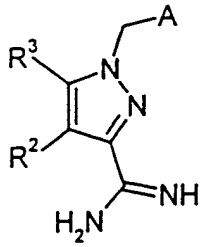
$R^{36'}$, $R^{37'}$, $R^{38'}$ and $R^{39'}$ have the meanings of R^{36}, R^{37}, R^{38} and R^{39} given above and are identical to or different from them, in Claim 1

R^{40} and R^{41} are identical or different and each represent hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring

in a palladium-catalysed reaction in inert solvents, ~~if appropriate in the presence of a base,~~

or

[D] amidines of the general formula (IX)

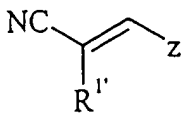


(IX),

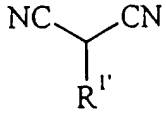
in which

A, R^2 and R^3 are each as defined above In Claim 1,

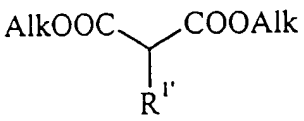
are reacted, ~~for example,~~ with compounds of the general formula (X), (Xa), (Xb) or (Xc)



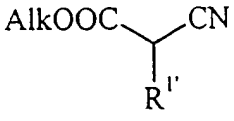
(X)



(Xa)



(Xb)



(Xc),

in which

$R^{1'}$ represents the optionally substituted cycloalkyl radical listed above under R^1;

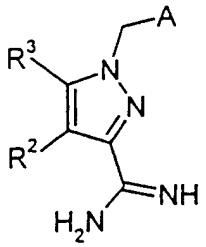
Alk represents straight-chain or branched alkyl having up to 8 carbon atoms, ~~preferably up to four carbon atoms;~~

and

Z represents an NH_2 group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbon atoms, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aroyloxy having 6 to 10 carbon atoms,

and, ~~if appropriate,~~ the substituents listed under X, Y, R^1, R^2, R^3 and/or A are modified or introduced by ~~customary methods, preferably by~~ acylation and derivatization of free amino groups, chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

7. Amidines of the general formula (IX)



(IX),

in which

R^2, R^3 and A are each as defined in one of the preceding Claims 1 to 3.

and their isomeric forms and salts.

8. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 & a pharmaceutically acceptable carrier

9. ~~Process for preparing medicaments, characterized in that at least one compound of the formula (I) according to Claim 1, if appropriate with customary auxiliaries and additives, is converted into a suitable administration form.~~ canceled

10. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 in combination with organic nitrates or NO donors.

11. Medicaments, comprising at least one compound of the general formula (I) according to Claim 1 in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).

12. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments.~~ canceled

13. A method of treating a ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of~~ cardiovascular diseases, comprising administering to a mammal an effective amount of a compound according to Claim 1.

14. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of~~ hypertension. The method of Claim 13, wherein said cardiovascular disease is

15. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of~~ A method of treating thromboembolic disorders and ischaemia comprising administering to a mammal an effective amount of a compound according to Claim 1

16. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments for the treatment of~~ sexual dysfunction. A method of treating

17. ~~Use of compounds of the general formula (I) according to Claim 1 for preparing medicaments~~ A method of treating inflammation, comprising administering to a mammal an effective amount of a compound according to Claim 1. having anti-inflammatory properties.

18. ~~Use according to any of~~ The method of Claims 13, 14, 15, 16 or 17 ~~12 to 17~~ where ~~the~~ compounds of the general formula (I) according to Claim 1 ~~are used~~ in combination with organic nitrates or NO donors ~~or in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).~~ in said is administered an